REMARKS

Claims 1-25 were pending in the present application. Of these, claims 7-19 and 21-23 have been withdrawn from consideration. By this Amendment, the specification and claim 24 each have been amended to correct a typographical error pointed out by the Examiner. No new matter has been introduced.

January 28, 2008 Office Action

Objections to the Specification and to Claim 24

The Office Action objected to the specification and claim 24, for containing typographical errors in the words "supernatants" and "administrable," respectively.

In response, Applicants have amended the specification and claim 24 to correct these errors. Applicants believe the above objections have been fully overcome and thus respectfully request their withdrawal.

Rejections Under 35 U.S.C. §112, second paragraph

In the Office Action, claims 24 and 25 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for reciting "a system for preventing or inhibiting growth of cancer cells." According to the Office Action, the specification does not define the term "system," and thus, the Office Action asserts that it is not clear exactly what a "system" is. In that regard, the Office Action asks whether it is an apparatus, a machine or a method, and notes

that method claims were not elected for prosecution at this time. The Office Action stated that the claims will be interpreted as composition claims.

The Office Action also rejected claims 24 and 25, asserting that the phrase "in combination with an intravenously administrable MTA for intravenous administration" is confusing. The Office Action questions the meaning of "an intravenously administrable MTA for intravenous administration," and suggests that the specification does not appear to provide any formulation suitable for intravenous administration. The Office Action noted that claim 24 depends on claim 1, which recites "MTA" and "combination with a biodegradable adhesive capable of adhering to tissue of a living subject."

In response, Applicants respectfully traverse the indefiniteness rejections noted above. Those of ordinary skill in the art would readily understand what is claimed when the claims are read in light of the specification. Thus, the claims fully comply with the requirements of 35 U.S.C. §112, second paragraph. In that regard, the term "system" as used in the claims is fully consistent with its use in the specification and thus, the specification provides sufficient context to render clear to one of ordinary skill in the art the claims reciting this term. Similarly, Applicants do not agree that the phrase referred to above with respect to intravenous administration of an MTA, is confusing or in any way indefinite within the meaning of Section 112. One of ordinary skill in the art clearly would understand what intravenous administration of an MTA is. Moreover, Applicants note that paragraph [0038] of the specification refers to such administration. Accordingly, for at least the reasons provided herein, the claims, as written, are not indefinite. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 24 and 25 under 35 U.S.C. §112, second paragraph.

Rejections Under 35 U.S.C. §103

Claims 1-6, 20, 24, and 25 were rejected under 35 U.S.C. §103, as allegedly being obvious over Calabresi, et al. (WO 01/397643 A2), in view of Filler, et al. (U.S. Pat. No. 6,919,067).

According to the Office Action, Calabresi teaches a method of inhibiting tumor growth in a mammal by administering to the mammal a composition comprising taurolidine, taurultam, or a biologically active derivative thereof. (The Office Action directed attention to the abstract, and page 1, lines 10-28). The Office Action stated that the composition (of Calabresi) is administered intravenously, topically, or by infusion (ID).

The Office Action also acknowledged that Calabresi does not expressly teach a composition comprising the claimed bioadhesive.

The Office Action asserted that Filler teaches a composition comprising a radiotherapeutic agent or agent that can be converted to a radio therapeutic, and a tissue glue. (The Office Action directed attention to the abstract). According to the Office Action, Filler further teaches the use of tissue glue as a matrix suitable for topical or other application to the locus of treatment (column 3, lines 28-50). The Office Action stated that tissue glue includes fibrin sealant matrix (column 9, lines 23-60). In the opinion expressed in the Office Action, it therefore would have been obvious to one of ordinary skill in the art to modify the composition of Calabresi using fibrin tissue glue matrix as a drug-loaded matrix to obtain the claimed invention, because (according to the Office Action) Filler teaches the use of fibrin glue matrix to provide controlled/delayed/slow release of therapeutic agent (column 9, lines 38-40; lines 66 through column 10, lines 1-30), Filler teaches the use of fibrin glue matrix as a carrier for

intravenous and topical formulations for the treatment of brain cancer (column 13, lines 54 through column 14, lines 1-54), and Calabresi teaches the desirability of preparing compositions comprising slow release matrix (page 13, line 21 through page 14, lines 1-6).

The Office Action also acknowledged that Calabresi does not explicitly teach the concentrations recited in claims 2-6. The Office Action asserted however, that "differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." The Office Action therefore concluded that it would have been obvious to one of ordinary skill in the art to, by routine experimentation, determine a suitable concentration that would fall within the claimed concentration. This, according to the Office Action, "is because Calabresi teaches the same method of administration suitable for the same treatment using the same therapeutic agent." Moreover, the Office Action asserted that "this is further because Fill [sic] teaches the use of fibrin glue is known in radiotherapeutic art to control/slow/delay the release of the therapeutic agent."

In response, Applicants respectfully traverse the obviousness rejections set forth in the Office Action. Applicants' claimed invention is directed to, *inter alia*, an antineoplastic composition comprising an antineoplastic-effective amount of a methylol transfer agent (MTA) in combination with a biodegradable adhesive capable of adhering to tissue of a living subject. First, notwithstanding the assertions made in the Office Action, Calabresi does not teach "the same method of administration suitable for the same treatment using the same therapeutic agent."

As the Office Action has acknowledged, Calabresi does not teach a composition comprising a bioadhesive capable of adhering to tissue of a living subject. There is no suggestion at all in Calabresi that the implantable matrices or other formulations referred to therein could or should incorporate an adhesive of any sort. Calabresi, therefore cannot teach or suggest the claimed "antineoplastically-effective amount of a of a methylol transfer agent (MTA) in combination with a biodegradable adhesive capable of adhering to tissue of a living subject." The Examiner's reliance on Filler to supply the missing claim features also falls short. Filler refers generally to agents, primarily radiotherapeutic agents, that can be useful with a tissue glue. Filler does not disclose the use of a methylol transfer agent (MTA), however, and thus, like Calabresi, cannot teach what an antineoplastically effective amount of such an agent would be in a formulation such as that claimed by the Applicants. Filler's general reference to agents (whether in a glue or not) useful in radio- and other therapies does not provide sufficient disclosure to allow one to successfully modify the Calabresi reference to arrive at the Applicants' invention. Applicants direct attention to the present specification, at paragraph [0016], for example, wherein it is noted that all anti-tumor agents are not identical in their modes of action or biological effects. In particular, it is noted that methylol transfer is to be contrasted with methyl transfer, a characteristic of many highly toxic anti-tumor drugs. Exemplified methylol transfer agents of the present application are described in the specification as having low toxicity and not having cytotoxicity against normal cells. The present invention allows the delivery of the drug in therapeutically effective concentrations with minimal toxic effects on healthy brain tissue. (See e.g. paragraph [0036]). The art of record simply does not allow one to reliably achieve this result. Therefore, as noted above, while Applicants maintain that one of ordinary skill in the art

would have no motivation to modify Calabresi's MTA formulations to incorporate a biodegradable adhesive, even if one were to attempt such modification, he could not expect to arrive successfully at the Applicants' claimed invention, simply on the additional teachings of the Filler reference. There is no guidance in any combination of teachings in the cited references that would lead one to conclude that a MTA would or even could be successfully employed in an amount that would be "anti-neoplastically effective" in the type of composition that is the subject of the Applicant's claimed invention. Thus, even if one were to combine teachings as the Office Action has done, there is no assurance that one could achieve an antineoplastic-effective amount of a methylol transfer agent (MTA) in combination with a biodegradable adhesive capable of adhering to tissue of a living subject, with mere routine experimentation or optimization of ranges.

Thus, notwithstanding the Office Action's statement to the contrary, this is not a case in which the general conditions of a claim are taught in the art, with only routine experimentation or optimization of ranges required to reach the specifics of the claim. For this reason alone, the claims are not obvious over the art cited in the Office Action.

Moreover, Applicants direct further attention to the important fact that the claims reflect the Applicants' unexpected findings that compositions containing the disclosed amounts of MTA release antineoplastically effective amounts of the agent over the entirety of the expected 14 day life span of a fibrin sealant matrix. This is discussed, for example, at paragraph [0054] and surrounding disclosure, (with specific effective ranges also recited at paragraph [0028]), and confirmed by the *in vitro* results described elsewhere in the Example. It is an extremely beneficial result in terms of the therapeutic efficacy of the claimed compositions, and is one

which cannot in any way be predicted from any of the prior art of record. The claims therefore are not rendered obvious by the art cited in the January 28, 2008 Office Action. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

Applicants believe all of the objections and rejections set forth in the January 28, 2008 Office Action have been overcome and the application is in condition for allowance. The Office is invited to telephone the undersigned if it is deemed to expedite prosecution.

Respectfully submitted,

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